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ORIGINAL ARTICLE

Ionic liquid promoted one pot approach for the synthesis of pyrido[1,2-c][1,3,5]thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones in water

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Thiadiazin-4-ones;
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Room temperature

Abstract A novel three component one pot methodology for rapid access to pyrido[1,2-c][1,3,5]thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones has been developed. A task specific ionic liquid [bmIm]SCN has been used as thiocyanating reagent. The reaction provides high yields of the product and proceeds at ambient reaction conditions in water. The use of water as the reaction medium and easy recyclability of the ionic liquid used as a reagent as well as promoter of the reaction endows the reaction with green aspects.

1. Introduction

Multicomponent reactions prove to be one of the key tools for efficient and speedy assembly of structurally complex and highly functionalized 'drug like' heterocycles as they provide a robust and straightforward approach toward the assembly using easily available starting materials (Jie et al., 2011; Domling and Ugi, 2000; Orru and de Greef, 2003; Sunderhaus and Martin, 2009). However, with the present paradigm focusing on green chemistry, there is a constant need for the development of operationally simple MCR methodologies that can promise benefits for organic syntheses in terms of atom economy, high yields and health and environmental safety, in a high throughput fashion. Water has emerged as a very desirable reaction media for organic syntheses because of its non-toxic, and environmentally benign nature. Very impressive results have been obtained during the last decade by implementing aqueous media in organic synthesis, specifically in the acceleration of MCR (Li, 2005; Pirrung and Sarma, 2004; Zonouz et al., 2012). The application of MCRs in water is a very promising field in synthetic chemistry (Dandia et al., 2012; Rajarathinam and Vasuki, 2012; Ma et al., 2010).

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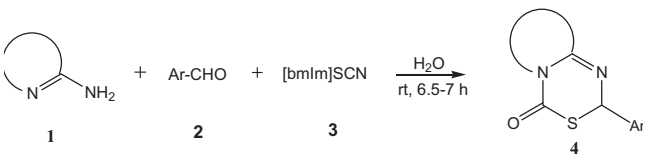
Room temperature ionic liquids have been attracting interest of synthetic community for a long period owing to their interesting properties like non-flammability, low vapor pressure, wide solvating ability and easy recyclability (Welton, 1999; Carlin and Wilkes, 1994).

The use of ionic liquids has broadened its scope from being only a reaction medium to performing its role as a catalyst and reagent (Wasserscheid and Keim, 2000; Brown et al., 2001; Leitner, 2003; Yang et al., 2003; Kumar and Pawar, 2004; Boon et al., 1986; Sheldon, 2001; Kim and Varma, 2005; Ranu and Jana, 2005; Zhu et al., 2005).

A novel task specific ionic liquid (TSIL) [bmIm]SCN (1-butyl-3-methylimidazolium thiocyanate) has been synthesized by Kamal and Chouhan (2005), which has proved excellent as a thiocyanating reagent. The use of metal thiocyanates, ammonium thiocyanate, trimethylsilyl isothiocyanate and many other reagents as thiocyanating reagents has been widely explored in the past. It has been observed that the low nucleophilicity of the SCN ion and poor stability of almost all the reagents used, render them rather unfit for use. Previous studies have also shown that the nucleophilicity of thiocyanate ion in [bmIm]SCN is much greater than that of KSCN in any ionic liquid (Kamal and Chouhan, 2005; Yadav et al., 2007; Gouda, 2013; Bacon and Guy, 1961; Pavlik et al., 1994; Nishiyama and Oba, 1987; Sasaki et al., 1981; Tamura et al., 1977; Burski et al., 1983; Iranpoor et al., 2000; Molina et al., 1982). The present protocol demonstrates the use of this ionic liquid as a reagent and a promoter of the reaction as well.

1,3,5-Thiadiazines and their derivatives are a significant class of biologically relevant heterocycles due to their anticancer (Temple et al., 1983), antimicrobial (Coburn et al., 1982; Chen et al., 1996), potential CNS (Malinka et al., 2002), antioxidant, antiprotozoal (Coro et al., 2011), and tuberculostatic (Zsolnai, 1968; Katiyar et al., 2003) properties. In addition, they are also used as herbicides (Chupp, 1973), insecticides (Nakaya et al., 1989) and miticides (Ikeda and Kanno, 1980). Pyridothiadiazine variants and thiazolothiadiazine variants particularly, have been reported in the literature to possess a wide range of biologically significant properties (Youssef et al., 2012; Neill et al., 1998; Dandia et al., 2004). One particular variant of pyridothiadiazine **PD 404182** has been known to show anti-HIV activity (Mizuhara et al., 2012). The established biological activities of these motifs combined with their interesting skeletal frameworks concur to classify them as intriguing synthetic exercises for organic chemists. Despite this fact, synthetic methodologies for their preparation have been very less explored till now.

In the light of the above mentioned facts and as a part of our ongoing work on the development of efficient methodologies to synthesize potentially bioactive heterocycles by eco-compatible methods (Siddiqui et al., 2003, 2010, 2012, 2013a–f), we herein report a novel and efficient strategy for the synthesis of potentially bioactive pyridothiadiazin-4-ones and thiazolothiadiazin-4-ones using 2-amino-heterocycles, aromatic aldehydes and [bmIm]SCN as starting materials. To the best of our knowledge, this is the first report on the use of TSIL [bmIm]SCN for heterocyclic synthesis. The reaction is promoted by ionic liquid and proceeds smoothly in water at room temperature to provide the target compounds in good to excellent yields (Scheme 1).



Scheme 1 Three component one-pot synthesis of pyrido[1,2-c][1,3,5]thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones.

2. Experimental

2.1. Methods and apparatus

The starting materials 2-aminopyridine, 2-aminothiazole, aromatic aldehydes, KSCN and ionic liquids [bmIm]Br and [bmIm]Cl are commercially available. The task specific ionic liquid [bmIm]SCN has been synthesized from ionic liquid [bmIm]OH according to a reported procedure (Yadav et al., 2007). Melting points were determined by the open glass capillary method (uncorrected). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II (400 MHz) FT spectrometer at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent. Chemical shifts are reported in parts per million relative to TMS as internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analysis was performed on an Elementar vario EL.

2.2. General procedure for synthesis of pyrido[1,2-c][1,3,5] thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones **4**

A mixture of 2-aminopyridine/2-aminothiazole **1** (1.0 mmol), aromatic aldehyde **2** (1.0 mmol) and [bmim]SCN **3** (2.0 mmol), and 2 mL of distilled water was taken in a 50 mL round-bottomed flask and stirred at rt for 6.5–7 h. After completion of the reaction as indicated by TLC, the product was extracted with ether (3 × 25 mL). The combined extracts were evaporated under reduced pressure to leave the crude product, which was purified by column chromatography to afford pure target compound **4**.

***4a**: 2-phenylpyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-181–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 4.3 (s, 1H), 5.01 (d, 1H), 5.77 (m, 1H), 6.51 (m, 1H), 7.28 (d, 1H), 7.06–7.14 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 61.0, 111.7, 122.6, 125.8, 127.1, 127.8, 128.8, 133.0, 141.3, 164.2; MS: m/z = 242 $[M]^+$ Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.41; H, 4.20; N, 11.54.

***4b**: 2-(4-chlorophenyl)pyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-191–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 4.1 (s, 1H), 5.5 (d, 1H), 5.80 (m, 1H), 6.62 (m, 1H), 7.31 (d, 1H), 7.00–7.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 61.5, 111.9, 122.9, 126.0, 129.2, 129.7, 132.7, 133.1, 139.1, 164.3; MS: m/z = 278 $[M]^+$ Anal. Calcd for $C_{13}H_9ClN_2OS$: C, 56.42; H, 3.28; N, 10.12. Found: C, 56.40; H, 3.30; N, 10.13.

***4c**: 2-p-tolylpyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-185–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 2.35 (s, 3H), 3.91 (s, 1H), 5.2 (d, 1H), 5.67 (m, 1H), 6.51 (m, 1H), 7.28 (d, 1H), 6.94–7.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 24.3, 61.1, 111.5, 122.3, 125.5, 127.7, 128.7, 132.7, 136.6, 138.0, 159.2; MS:

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m/z = 256 $[M]^+$ Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.62; H, 4.69; N, 10.90.

***4d**: 2-(3-nitrophenyl)pyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* Yellow solid, mp-196–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 4.6 (s, 1H), 5.5 (d, 1H), 5.80 (m, 1H), 6.61 (m, 1H), 7.35 (d, 1H), 7.40–8.00 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 61.6, 112.3, 122.9, 123.0, 126.2, 129.7, 133.2, 133.9, 141.9, 148.4, 164.5; MS: m/z = 287 $[M]^+$ Anal. Calcd for $C_{13}H_9N_3O_3S$: C, 54.35; H, 3.16; N, 14.63. Found: C, 54.31; H, 3.18; N, 14.66.

***4e**: 2-(2-chlorophenyl)pyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-194–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.31 (s, 1H), 5.32 (d, 1H), 5.71 (m, 1H), 6.51 (m, 1H), 7.29 (d, 1H), 7.00–7.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 51.9, 111.9, 122.8, 125.8, 126.9, 128.4, 129.1, 129.8, 132.9, 133.6, 164.3; MS: m/z = 276 $[M]^+$ Anal. Calcd for $C_{13}H_9ClN_2OS$: C, 56.42; H, 3.28; N, 10.12. Found: C, 56.40; H, 3.32; N, 10.15.

***4f**: 2-(4-(trifluoromethyl)phenyl)pyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-191–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 4.43 (s, 1H), 5.41 (d, 1H), 5.82 (m, 1H), 6.68 (m, 1H), 7.46 (d, 1H), 7.02–7.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 61.5, 111.3, 122.8, 124.2, 125.2, 125.8, 128.1, 129.3, 132.5, 144.3, 164.1; MS: m/z = 310 $[M]^+$ Anal. Calcd for $C_{14}H_9F_3N_2OS$: C, 54.19; H, 2.92; N, 9.03. Found: C, 54.22; H, 2.90; N, 9.05.

***4g**: 2-(3,4-dimethoxyphenyl)pyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-197–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 3.73 (s, 6H), 3.97 (s, 1H), 5.09 (d, 1H), 5.71 (m, 1H), 6.40 (m, 1H), 6.46–6.54 (m, 3H), 7.45 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 56.2, 61.4, 111.1, 112.8, 115.3, 121.1, 122.2, 125.7, 133.0, 134.1, 148.2, 149.8, 163.6; MS: m/z = 302 $[M]^+$ Anal. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.62; H, 4.70; N, 9.23.

***4h**: 2-(2-chlorophenyl)-7-methylpyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-196–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 1.71 (s, 3H), 4.32 (s, 1H), 5.13 (d, 1H), 6.30 (m, 1H), 7.06 (d, 1H), 7.01–7.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 19.5, 51.9, 122.0, 122.6, 124.8, 126.9, 128.2, 128.9, 129.5, 133.1, 137.9, 141.4, 164.4; MS: m/z = 290 $[M]^+$ Anal. Calcd for $C_{14}H_{11}ClN_2OS$: C, 57.83; H, 3.81; N, 9.63. Found: C, 57.81; H, 3.77; N, 9.59.

***4i**: 7-methyl-2-p-tolylpyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 1.71 (s, 3H), 2.35 (s, 3H), 4.10 (s, 1H), 5.11 (d, 1H), 6.23 (m, 1H), 6.81–6.94 (m, 4H), 7.01 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 19.5, 24.3, 51.6, 121.7, 122.2, 124.2, 127.7, 129.1, 136.2, 137.1, 138.0, 164.1; MS: m/z = 270 $[M]^+$ Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.60; H, 5.19; N, 10.41.

***4j**: 2-phenylthiazolo[3,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-134–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 4.1 (s, 1H), 5.64 (d, 1H), 7.20 (s, 1H), 7.06–7.14 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 59.5, 100.1, 127.2, 127.9, 128.8, 131.5, 141.0, 163.2, 164.6; MS: m/z = 248 $[M]^+$ Anal. Calcd for $C_{11}H_8N_2OS_2$: C, 53.20; H, 3.25; N, 11.28. Found: C, 53.23; H, 3.27; N, 11.30.

***4k**: 2-p-tolylthiazolo[3,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 2.35 (s, 3H), 5.58 (d, 1H), 7.11 (s, 1H), 6.80–6.94 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 24.6, 59.3, 100.0, 127.7, 129.1, 131.3, 136.6, 138.0, 162.8, 164.1; MS: m/z = 262 $[M]^+$ Anal. Calcd for $C_{12}H_{10}N_2OS_2$: C, 54.94; H, 3.84; N, 10.68. Found: C, 54.91; H, 3.80; N, 10.69.

***4l**: 2-(2-chlorophenyl)-6-methylthiazolo[3,2-c][1,3,5]thiadiazin-4(2H)-one:* Brownish solid, mp-137–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 1.71 (s, 3H), 4.33 (s, 1H), 5.42 (d, 1H), 7.03–7.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 18.4, 50.4, 101.8, 126.9, 128.6, 129.2, 129.9, 133.1, 140.5, 141.4, 163.1, 164.7; MS: m/z = 296 $[M]^+$ Anal. Calcd for $C_{12}H_9ClN_2OS_2$: C, 48.56; H, 3.06; N, 9.44. Found: C, 48.60; H, 3.09; N, 9.41.

2.3. Recovery of the ionic liquid

The ionic liquid [bmIm]SCN used in this protocol could be easily recycled and reused for several reaction cycles without any considerable effect on its reactivity or yield of the product (Fig. 1). After the completion of the reaction, the remaining ionic liquid [bmIm]OH in the vessel was dissolved in acetone (10 mL) and treated with conc. HCl (1.2 equiv). The mixture was then treated with KSCN (2 equiv) at rt and stirred for 48 h. The resulting suspension was filtered and the filtrate was subjected to a vacuum to remove volatile material. The residue was dissolved in dichloromethane and again filtered. The filtrate was dried using anhydrous sodium sulfate. Finally, upon concentration under vacuum at 70 °C, 1-*n*-butyl-3-methylimidazolium thiocyanate ([bmIm]SCN) was obtained as a red colored liquid. This could be used for the reactions for up to four reaction cycles without any appreciable loss of its catalytic efficiency.

1-Butyl-3-methylimidazolium thiocyanate: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 0.93 (t, 3H, J = 7.7 Hz), 1.22–1.43 (m, 2H), 1.83–2.05 (m, 2H), 3.98 (s, 3H), 4.12 (t, 2H, J = 7.7 Hz), 7.60 (s, 1H), 7.55 (s, 1H), 8.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 13.8, 20.2, 33.3, 36.4, 52.5, 121.0, 125.4, 143.4; MS: m/z = 139 [M^+-SCN].

3. Results and discussion

3.1. Effect of solvent

Our study commenced with stirring the reaction mixture of 2-aminopyridine **1a**, benzaldehyde **2a** and KSCN as model substrates, in various solvents at room temperature. The results are summarized in Table 1.

We performed a screening of various solvents such as EtOH, MeOH, DCM, Et_2O, and H_2O (Table 1, entries 1–6). The results of Table 1 reveal that unsatisfactory yields were obtained in all the solvents we used. Although water was found to be the better solvent for carrying out the reaction, the yields

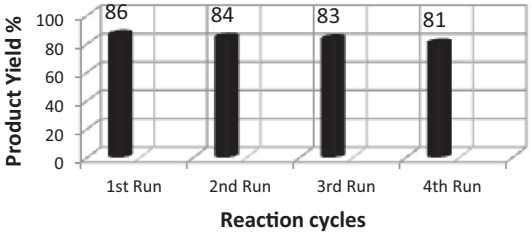
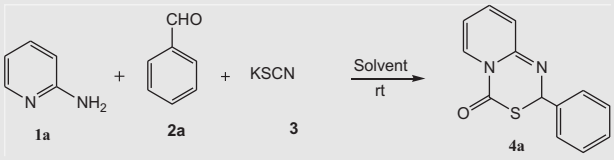


Figure 1 Recycling and reuse of bmIm[SCN].

Table 1 Screening of the solvent for the synthesis of compound **4a.**[a]



Entry	Solvent	Temp.	Time (h)	Yield[b] (%)
1	EtOH	rt	10	19
2	MeOH	rt	10	20
3	DCM	rt	10	28
4	Et_2O	rt	10	20
5	H_2O	rt	10	40
6	H_2O	Reflux	6	25

[a] Reaction conditions: 2-aminopyridine **1a** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), KSCN **3** (1.0 mmol), solvent (2 mL).
[b] Isolated yields after purification.

were still not very pleasing (Table 1, entry 5). We then tried subjecting the reaction to a higher temperature for the improvement in the yield in the presence of water but it was observed that higher temperature had an adverse effect on the reaction and we obtained even lesser yield of 25% (Table 1, entry 6). Besides, side products were also observed in the TLC observed after the completion of the reaction.

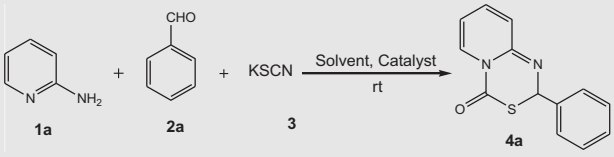
3.2. Effect of catalysts

Our next venture was to examine if the reaction was positively affected by employing a catalyst. For this examination, various effective lewis acid catalysts were employed and tested. We achieved a slight improvement in the yield of the product, but the results were still not very satisfactory (Table 2). CuI proved to be a better catalyst of all the catalysts used (Table 2, entry 6). The increase in the amount of CuI, however did not affect the yield in any way (Table 2, entry 7).

3.3. Effect of thiocyanating reagent

Based on the ever-increasing and promising use of ionic liquids as reaction media and catalysts in organic syntheses these days, we investigated the yields of the reaction product using KSCN in the presence of imidazolium based ionic liquids [bmIm]Br {1-butyl-3-methylimidazolium bromide} and [bmIm]Cl {1-butyl-3-methylimidazolium chloride}(Table 3, entries 1 and 2). The yields obtained were better than before. Encouraged by this result and persuaded by the reports on the successful use of TSIL [bmIm]SCN as a reagent (Kamal and Chouhan, 2005; Yadav et al., 2007; Gouda, 2013), we decided to use it as the thiocyanating reagent as well as the reaction medium. The yields obtained were better than before but not as high as expected (Table 3, entry 3). Based on the optimization in Table 1 and keeping in mind the fact that water is known to accelerate multicomponent reactions and also plays a role in increasing the catalytic efficiency of ionic liquids (Wolfson

Table 2 Influence of various catalysts on the synthesis of compound **4a.**[a]



Entry	Solvent	Catalyst (mol%)	Time (h)	Yield[b] (%)
1	H_2O	$InBr_3$(10)	8	42
2	H_2O	$SnCl_2$(10)	8	40
3	H_2O	$ZnCl_2$(10)	8	33
4	H_2O	$FeCl_3$(10)	8	46
5	H_2O	$FeBr_3$(10)	8	49
6	H_2O	CuI(10)	8	50
7	H_2O	CuI(15)	8	50

[a] Reaction conditions: 2-aminopyridine **1a** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), KSCN **3** (1.0 mmol), solvent (2 mL).
[b] Isolated yields after purification.

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Table 3 Screening of ionic liquid and thiocyanating reagent for the synthesis of compound **4a**.

Entry	Solvent	Thiocyanating reagent	Temp.	Time (h)	Yield[a] (%)
1	[bmIm]Br	KSCN	rt	7	48
2	[bmIm]Cl	KSCN	rt	7	50
3	–	[bmIm]SCN	rt	7	59
4	H_2O	[bmIm]SCN	rt	7	86

[a] Isolated yields after purification.

et al., 2005), we then decided to use water as the reaction medium. To our delight, we were successful in achieving excellent yields at room temperature under only 7 h of reaction time without the use of any other catalyst (Table 3, entry 4). Furthermore, the avoidance of the use of any catalyst proved that ionic liquid is not only playing the role of a reagent but also catalyzing the reaction.

3.4. Effect of reaction temperature

After achievement of efficient access to the target compound **4a**, the reaction was carried out at varying temperatures (Table 4). Interestingly, mild reaction conditions provided better yields of the product. The results clearly indicated that the reaction was most efficient at room temperature (Table 4, entry 1).

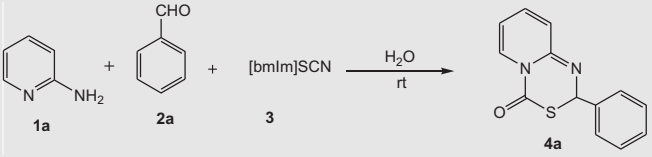
3.5. Synthesis of derivatives of pyrido[1,2-c][1,3,5]thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones

With the optimized conditions in hand, we then explored the scope of the process by using various variants of 2-aminopyridines, 2-aminothiazoles and aromatic aldehydes, our aim being to determine the generality of the route. The results are summed up in Table 5.

It is quite clear from Table 5 that all the variants were tolerated well by the reaction. However, aldehydes with electron withdrawing groups proved more beneficial for the reaction.

Based on the experimental results, a mechanism for the course of the reaction has been proposed (Scheme 2). The first step of the reaction involves Schiff's base formation between 2-amino derivative and aromatic aldehyde to give the imine derivative, which then undergoes nucleophilic attack by the thiocyanate ion from [bmIm]SCN to give an intermediate. This intermediate then undergoes intramolecular attack on the nitrile group leading to cyclization and finally hydrolysis to yield the target compound **4**. [bmIm]SCN supposedly plays its catalytic role throughout the reaction by activating the electrophilic centers. The reaction results in the formation of the ionic liquid [bmIm]OH {1-butyl-3-methylimidazolium hydroxide}, which is a precursor to our TSIL [bmIm]SCN and it can be re-synthesized from the recovered [bmIm]OH, thus providing for the recyclability of the ionic liquid. Water is crucial for the reaction since it also provides for the recyclability of the ionic liquid [bmIm]SCN.

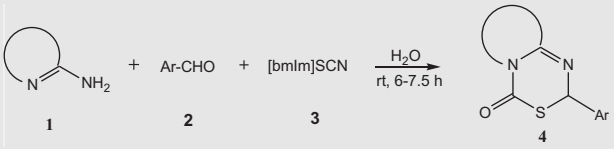
Table 4 Optimisation of temperature for the synthesis of compound **4a.**[a]



Entry	Temp (°C)	Time (h)	Yield[b] (%)
1	rt	7	86
2	35	7	80
3	40	7	70
4	60	7	62
5	80	7	50

[a] Reaction conditions: 2-aminopyridine **1a** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), [bmIm]SCN **3** (2.0 mmol), H_2O (2 mL).
[b] Isolated yields after purification.

Table 5 Influence of variants of aromatic aldehydes, 2-aminopyridine and 2-aminothiazole on the synthesis of compound **4**.[a]



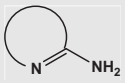
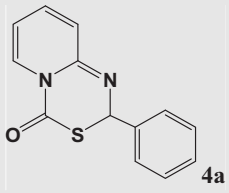
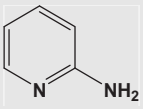
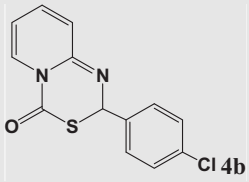
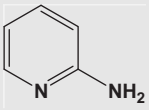
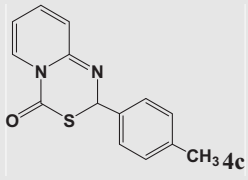
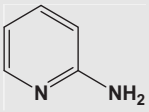
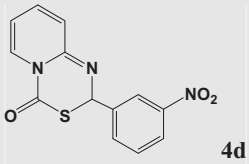
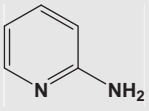
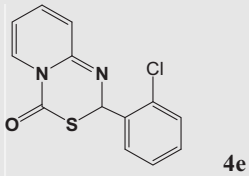
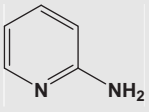
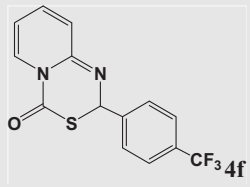
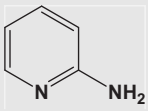
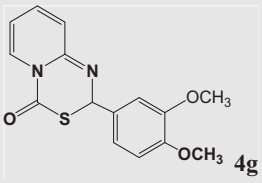
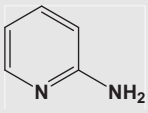
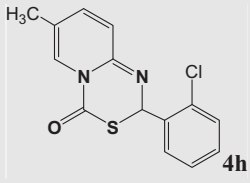
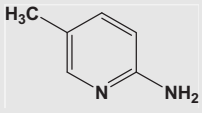
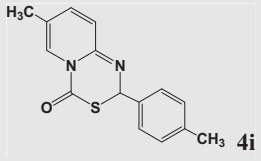
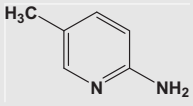
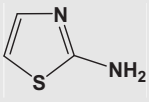
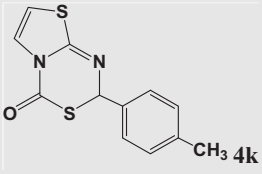
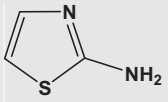
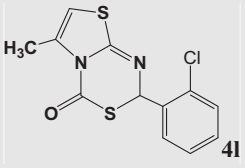
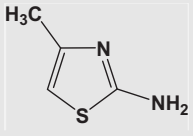
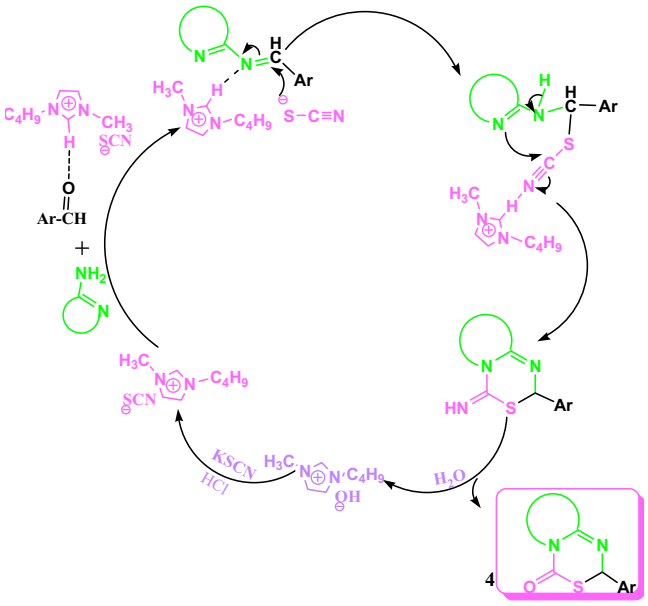
Product	Ar		Time (h)	Yield[b] (%)
 **4a**	H		6	86
 **4b**	4-Cl		6	90
 **4c**	4-CH_3		7.5	80
 **4d**	3-NO_2		6.5	87
 **4e**	2-Cl		6.5	87

Table 5 (*continued*)

 **4f**	4-CF_3		6	90
 **4g**	3,4-$(OCH_3)_2$		7.5	76
 **4h**	2-Cl		7	88
 **4i**	4-CH_3		7	80
 **4j**	H		6.5	85
 **4k**	4-CH_3		7	82
 **4l**	2-Cl		7	88

[a] Reaction conditions: 2-aminopyridine **1a** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), [bmIm]SCN **3**(2.0 mmol), solvent (2 mL).
[b] Isolated yields after purification.



Scheme 2 Postulated mechanism for the synthesis of compound **4**.

4. Conclusion

In summary, we have developed an efficient protocol for the synthesis of pyrido[1,2-c][1,3,5]thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones in water by the use of task specific ionic liquid [bmIm]SCN as a thiocyanating reagent. In addition to the high speed, excellent yields, simple methodology and its powerful capability to form 2 new N—C and one S—C bond in a one-pot fashion, the protocol can be applied to a range of substrates demonstrating its effectiveness for the synthesis of many compounds.

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References

Bacon, R.G.R., Guy, R.G., 1961. J. Chem. Soc., 2428–2447.
Boon, J.A., Levinsky, S.A., Pflig, J.L., Wilker, J.S., 1986. J. Org. Chem. 51, 480.
Brown, R.A., Pollet, P., Mckoon, E., Eckert, C.A., Liotta, C.L., Jessop, D.G., 2001. J. Am. Chem. Soc. 123, 1254–1255.
Burski, J., Kiesowski, J., Michalski, J., Pakulski, M., Skowronska, A., 1983. Tetrahedron 39, 4175.
Carlin, R. T.; Wilkes, J. S. 1994. In Advances in Nonaqueous Chemistry; Mamantov, G., Popov, A., Eds.; VCH Publishing: New York.
Chen, G., Zou, J., Song, X., Li, Y., Yaoxue Xuebao, 1996. Chem. Abstr. 31, 425.
Chupp, J. P. U.S. Patent 3 741 964, 1971; *Chem. Abstr*. 1973, *79*, 78857.
Coburn, R.A., Ho, C.-H., Bronstein, M.L., 1982. J. Med. Chem. 25, 481.
Coro, J., Piñeiro, R., Monzote, L., Rodríguez, H., Suárez, M., 2011. Open Med. Chem. J. 5, 51–60.
Dandia, A., Arya, K., Sati, M., Gautam, S., 2004. Tetrahedron 60, 5253–5258.
Dandia, A., Laxkar, A.K., Singh, R., 2012. Tetrahedron Lett. 53, 3012–3017.
Domling, A., Ugi, I., 2000. Angew. Chem. Int. Ed. 39, 3168–3210.
Gouda, M.A., 2013. Synth. Comm. 43, 1–28.
Ikeda, K.; Kanno, H. Jpn. 80 13 211, 1980; *Chem. Abstr*. 93, 46729.
Iranpoor, N., Firouzabadi, H., Shaterian, H., 2000. Synlett 10, 65.
Jie, Y., Feng, S., Liu-Zhu, G., 2011. Acc. Chem. Res. 44, 1156–1171.
Kamal, A., Chouhan, G., 2005. Tetrahedron Lett. 46, 1489–1491.
Katiyar, D., Tiwari, V.K., Tripathi, R.P., Srivastava, A., Chaturvedi, V., Srivastava, R., Srivastava, B.S., 2003. Bioorg. Med. Chem 11, 4369–4375.
Kim, Y.S., Varma, R.S., 2005. Tetrahedron Lett. 46, 7447–7449.
Kumar, A., Pawar, S.S., 2004. J. Org. Chem. 69, 1419–1420.
Leitner, W., 2003. Nature 423, 930–931.
Li, C.-J., 2005. Chem. Rev. 105, 3095.
Ma, N., Jiang, B., Zhang, G., Tu, S.J., Wever, W., Li, G., 2010. Green Chem. 12, 1357–1361.
Malinka, W., Kaczmarz, M., Filipek, B., Sapa, J., Glod, B., 2002. Il Farmaco. 57, 737–746.
Mizuhara, T., Oishi, S., Ohno, H., Shimura, K., Matsuokab, M., Fujii, N., 2012. Org. Biomol. Chem. 10, 6792–6802.
Molina, P., Alajarin, M., Ferao, A., Lindon, M.J., Fresneda, P.M., Vilaplana, M.J., 1982. Synthesis, 472.
Nakaya, M.; Fukushi, Y.; Shiraishi, S.; Nakamura, M.; Numata, S.; Kodaka, K.; Ooka, M. EP 308 961, 1989. *Chem. Abstr*. 111, 174137.
Neill, C.G., Preston, P.N., Wightman, R.H., 1998. Tetrahedron 54, 13645–13654.
Nishiyama, K., Oba, M., 1987. Bull. Chem. Soc. Jpn. 60, 2692.
Orru, R.V.A., de Greef, M., 2003. Synthesis, 1471–1499.
Pavlik, J.W., Tongcharoensirikul, P., Bird, N.P., Day, A.C., Barltrop, J.A., 1994. J. Am. Chem. Soc. 116, 2292–3000.
Pirrung, M.C., Sarma, K.D., 2004. J. Am. Chem. Soc. 126, 444–445.
Rajarathinam, B., Vasuki, G., 2012. Org. Lett. 14, 5204–5206.
Ranu, B.C., Jana, R., 2005. J. Org. Chem. 70, 8621.
Sasaki, T., Nakanishi, A., Ohno, M., 1981. J. Org. Chem. 46, 5445–5447.
Sheldon, R., 2001. Chem. Commun., 2399–2407.
Siddiqui, I.R., Singh, P.K., Singh, J., Singh, J., 2003. J. Agric. Food Chem. 51, 7062–7065.
Siddiqui, I.R., Singh, A., Shamim, S., Srivastava, S., Singh, P.K., Yadav, S., Singh, R.K.P., 2010. Synthesis 10, 1613–1616.
Siddiqui, I.R., Shamim, S., Kumar, D., Shireen, Waseem, M.A., 2012. New J. Chem. 36, 2209–2214.
Siddiqui, I.R., Shireen, Shamim, S., Abumhdi, A.A.H., Waseem, M.A., Srivastava, A., Rahila, Srivastava, A., 2013a. New J. Chem. 37, 1258–1263.
Siddiqui, I.R., Waseem, M.A., Shamim, S., Shireen, Srivastava, A., Srivastava, A., 2013b. Tetrahedron Lett. 54, 4154–4158.
Siddiqui, I.R., Abumhdi, A.A.H., Shamim, S., Shireen, Waseem, M.A., Rahila, Srivastava, A., Srivastava, A., 2013c. RSC Adv. 3, 10173–10176.
Siddiqui, I.R., Srivastava, A., Shamim, S., Srivastava, A., Shireen, Waseem, M.A., Rahila, Srivastava, A., Rai, P., Singh, R.K.P., 2013d. Asian J. Org. Chem. 2, 519–524.
Siddiqui, I.R., Shamim, S., Waseem, M.A., Srivastava, A., Rahila, 2013e. RSC Adv., DOI: http://dx.doi.org/10.1039/C3RA42159G.
Siddiqui, I.R., Shireen, Shamim, S., Waseem, M.A., Abumhdi, A.A.H., Srivastava, A., Srivastava, A., 2013f. Tetrahedron Lett. 54, 5083–5086.
Sunderhaus, J.D., Martin, S.F., 2009. Chem. Eur. J. 15, 1300–1308.
Tamura, Y., Kawasaki, T., Adachi, M., Tanio, M., Kita, Y., 1977. Tetrahedron Lett. 18, 4417.
Temple, C., Wheeler, G.P., Comber, R.N., Elliot, R.D., Montgomery, J.A., 1983. J. Med. Chem. 26, 1641.
Wasserscheid, P.J., Keim, W., 2000. Angew. Chem. Int. Ed. 39, 3772–3789.
Welton, T., 1999. Chem. Rev. 99, 2071–2083.

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Wolfson, A., Vankelecomb, I.F.J., Jacobsb, P.A., 2005. Tetrahedron Lett. 46, 2513–2516.
Yadav, L.D.S., Patel, R., Rai, V.K., Srivastava, V.P., 2007. Tetrahedron Lett. 48, 7793–7795.
Yang, X.F., Wang, M.W., Li, C., 2003. J. Org. Lett. 5, 657–660.
Youssef, A.M.S., Azab, M.E., Youssef, M.M., 2012. Molecules 17, 6930–6943.
Zhu, A.L., Jiang, T., Wang, D., Han, B.X., Liu, L., Huang, J., Zhang, Z.C., Sun, D.H., 2005. Green Chem. 7, 514–517.
Zonouz, A.M., Eskandari, I., Moghani, D., 2012. Chem. Sci. Trans. 1, 91–102.
Zsolnai, T., 1968. Arzneimittelforschung 18, 1319–1324.

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